

## Discussion

# Discussion to ‘Sex differences in the hypothalamus in the different stages of human life’ by Dick F. Swaab et al.

### Pfaff

What is the neuroanatomy of aggression and what would you study to show the sex differences in that?

### Swaab

As all functions, this function is not localized in one particular system; several systems seem to be important, for instance, the cholinergic, and septum. In any structure, in any transmitter, there are sex differences. Androgen receptors are present in quite a number of areas, including the amygdala. It is very difficult to find an objective measure for aggressiveness.

### Finch

A question about your targeting the physical aggression among young males. Is this also true among adolescent male chimpanzees and bonobos?

### Swaab

Certainly not bonobos.

### Finch

It is very clear that in that particular non-human primate, which is female-dominated of course, the levels of adolescent aggression are very much lower. You have these marvelous sex differences in structures, like the bed nucleus of the stria terminalis, which have been correlated with the vasopressin effects on aggression in animals. So, is the bed nucleus the solution?

### Swaab

We do not know if this nucleus is related to aggressive behavior in human beings. It is very difficult to do this type of studies.

### Kessler

A number of years ago, I was involved in a study in Finland among a number of very highly aggressive, violent crimi-

nals, who were compared with a normal control population. This was a hyper aggressive group versus a non-aggressive group. We found in the CSF low levels of serotonin. The thought was that serotonin is involved in aggression. Aggressive impulsive disorders got quite a lot of currency in the psychiatric literature, particularly in the frontal cortex.

### Swaab

There are so many systems involved, for instance, there is also a very clear seasonal rhythm in certain types of aggression, certain types of murders. We have done some studies in this field. Aggression is going up in summer and is lower in winter. This indicates that also the suprachiasmatic nucleus is involved. The suprachiasmatic nucleus is influencing the serotonergic system very strongly.

### Buitelaar

I think the problem is that there is a huge difference in aggression between males and females, the major risk factor for aggression is the male gender. But, within males, there is only a modest correlation between the levels of androgens, testosterone and so on, and aggression. This is the same within females. So, within the gender, the correlations are quite modest; and, also, to some extent, contradictory. That should challenge us to look at other issues, like serotonin or the relationship between hormonal systems and neurotransmitter systems.

### Swaab

This does not exclude androgen as a very important factor, because during development there might be a difference, which is organizing the brain in such a way that a person is more sensitive to androgens for the rest of his life. So, the levels in adulthood do not tell very much.

### Buitelaar

But there are also some data from children. What would be your recommendation, which one of all psychiatric and neurological diseases should be a target for more focus on gender-related issues. It is for the whole psychiatry, it is

from schizophrenia to depression, to Alzheimer, to childhood disorders like autism, etc.

### **Swaab**

Schizophrenia is a very good example. It is more prevalent in males, but it is also more serious in its symptoms. So the question is whether sex hormones are important in this type of disorders. Of course in schizophrenia we know that, although it is probably a developmental disorder, which has its roots already during halfway gestation; the signs and symptoms become only overt in puberty, during the period when the sex hormones are going to circulate. So, I think it is important to relate sex hormone levels in the various periods of our life to the risk and also the signs and symptoms of diseases and then see whether we can influence the disease by influencing the sex hormone levels.

### **Buitelaar**

In relation to this, the age of onset of schizophrenia is much later in women, generally. The very early onset cases are mostly among boys.

### **Heuser**

It has been shown in large epidemiological studies that there are two peaks of first onset of schizophrenia in women, the very early adulthood, and after or during menopause. So, it seems to be a very complicated issue what sex hormones are doing.

### **Brosens**

Is it true that most women who are in prison have committed their crime at the time of menstruation? If that is true, it may well be that it is not the hormones as such, but the changes in the hormones may be more important.

### **Swaab**

I know some publications on the menstrual cycle in causing accidents, also by female pilots, who appear to be more at risk during the menstrual period, but those are only slight effects.

### **Slob**

You seemed to reach the conclusion that social factors do not play a role and if I remember correctly, there are many cases where sex has been reassigned very early after birth, and there were very successful reassignments. But we never heard about those people.

### **Swaab**

Sex reassignment can be successful, that is true. This is occurring on the basis of the anatomy, the sex organs are more male or female. But, there are certainly a proportion

of the children who are sex-assigned in the wrong way. That is, the sex organs are anatomically okay, but the brain has developed in a different direction. It is amazing how little follow-up research has been done in this field.

### **Pfaff**

You mentioned very briefly SRY expression of the brain [1]. I would like to mention that there were several manuscripts on Müllerian inhibiting substance receptor expression in the brain and one wonders why this receptor was being expressed if MIS is not circulating to the brain. What causal share would you give these non-hormonal, genetic factors to the sexual differentiation of the brain and are you aware of any functional evidence that the expression of these genes might be important.

### **Swaab**

The Reisert group in Ulm has shown that if you take out pieces of rat brain and culture it without sex hormones, there are certain cells, dopaminergic cells, which differentiate in male or in female direction. This is also a functional difference, those cells produce dopamine, they are sexually dimorphic independent of hormones in the medium. That was the start of thinking about of non-receptor mediated sexual differentiation.

I do not know if I can give an estimate of the importance of this type of factors. If I would go over the human literature, I would say that aromatization is not very important for gender. That would be a first conclusion. If we look into that literature, we can say that testosterone is important, remember the risk in children with congenital adrenal hyperplasia, for instance. But it is certainly not the only factor, because there is just a higher risk. The majority has no gender problems. I think we should not make statements about sexual differentiation of 'the' brain, because every region in the brain, every cell type, has got its own life history, and it might well be that in one part of the brain aromatization is important, but that in another part it is direct genomic factors.

### **Finch**

In humans there is one birth at a time in general and it is a boy or a girl. In rodents however, the picture of gender differentiation is much more of a continuum than a dichotomy in adult behaviors. Of course, being interested in human behavior, we settle on dichotomies more than continua. However, in some cases, a remarkable overlap in the categorized behavioral groups can be seen.

### **Swaab**

This point is very important on the thinking of sex reassignment, in children in which the doctors are in doubt about their sex. Thus far, there is a very strong push from society, from the medical society, from the parents to make a decision, it does not matter what, it should be either a

boy or a girl. I think that, if the doubt is so strong, it would make sense to postpone the decision until the child itself can tell us what direction the brain has taken. So, in those cases we should try not to think in male–female, but just human, and wait a little bit. However, the idea that you could leave a child without assigning it to be a boy or a girl for some years, is appalling for most people. But I think it is the best solution, you should not make a mistake that is so detrimental for the rest of the life of the child.

### **Brosens**

Until what age postpone the decision?

### **Swaab**

Around the age between 4 and 6, the child can perfectly make clear what direction the brain has taken.

### **Finch**

Sex is not a classification but an equation with terms and customs applied to those terms and maybe even a formula.

### **Swaab**

You should tell that to the surgeons.

### **Slob**

Maybe I am the only one having difficulties with your suggestion to wait until the age of 4–6 years. I think it is really hard to deal with a child not knowing whether it is a boy or a girl. The child goes to kindergarten and it is not known whether it is a boy or a girl. Tremendous social-psychological problems might evolve. I hope you have some examples of individuals that were treated that way and became—forgive me—normal adults.

### **Swaab**

I am sure it will cause tremendous stress for the parents and for the child, but think about the stress for the rest of their lives if surgery is not done in the right direction.

### **Slob**

I believe we have ample possibilities to really make the proper decision with all the genetic markings that are available to make the best guess. In medicine we always make mistakes.

### **Swaab**

In many cases you can, but there is a small group in which there is serious doubt and if you ask for examples, I can

quote the work of Cohen-Kettenis [2], who is working on transsexuals in general, but also children.

### **Slob**

Maybe your suggestion should be: postpone the operation, because that is more or less definite. But be open about the possibilities and make a choice, the best choice you can make then and leave it open to a certain extent.

### **Swaab**

That would be a big step forward. Also because I think that society cannot influence the process anyhow.

### **De Kloet**

What kind of directions do you envision that this type of work should go: measure more, measure better with neuropsychology, to find out better the type of signaling pathways, postmortem brains, just to mention a few things?

### **Swaab**

I agree with you it is meager in the sense that we do not know anything about mechanism. But we should focus on specific diseases, for instance, eating disorders, a tremendously important field. So far, the focus has only been on society. Girls who do not eat are anorexic because they want to be as beautiful as the models in the newspapers, that was the idea. But there is an observation of a blind girl that had anorexia nervosa at the age of 18, with all the signs and symptoms and she had never seen the models around. There are many indications that this is a disease of the hypothalamus and it is sexually dimorphic.

### **Goodwin**

This takes us to the issue how we start to fill in the gap between structural dichotomism on one hand and either behavior or illness variables on the other.

## **References**

- [1] Sibug R, Koppers E, Beyer C, Maxson SC, Pilgrim C, Reisert I. Genotype-dependent sex differentiation of dopaminergic neurons in primary cultures of embryonic mouse brain. *Brain Res Dev Brain Res* 1996;93:136–42.
- [2] Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatr* 2001;40:472–81.